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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,943	07/11/2001	Avi Ashkenazi	10466/88	1367

35489 7590 02/06/2004

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,943	ASHKENAZI ET AL.	
	Examin r	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

The amendment after final filed 10/02/03 had been entered as indicated on the Advisory Action mailed 11/06/03. The amendment raised no new grounds of rejection.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Response to Amendment

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection under 35 USC 112, second paragraph, is withdrawn after further consideration.

The Declaration under 37 CFR 1.132 filed 10/02/03 is insufficient to overcome the rejection of claims 39-44 based upon 35 USC 101 and 112, first paragraph, as set forth in the last Office action because: It is maintained for the reasons of record that gene amplification does not provide utility for an antibody that binds the protein encoded by the gene of interest because it is unknown if gene number increase for PRO 339 corresponds to expression of the encoded protein as previously discussed (*e.g.*, pages 4-5 of Final Office Action). Also, there is no evidence that clinicians use information about a gene product not-being overexpressed as a basis for deciding not to treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification. If the nucleic acid encoding the PRO protein had utility, the antibody that binds the protein would not because it cannot be used diagnostically (see Advisory Action). The maintenance of the rejections is further addressed below under the 35 USC 101 rejection.

Claim Rejections - 35 USC § 101/112, First Paragraph

Claims 39-44 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action (paper #16) on pages 4-5 and discussed in the Advisory action.

Claims 39-44 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's request for reconsideration and subsequent reconsideration by the Examiner has not changed the rejection of the claims previously set forth under 35 USC 101 and 112, first paragraph. Although, it is now conceded that the gene amplification assay provides a patentable utility for the PRO339 nucleic acid. However, the instant application has claims directed to PRO339 antibodies. Applicant argued that the utility of the PRO339 nucleic acid carries over to the polypeptide and antibody claims. Specifically, Applicant argued that there is an assumption

of utility unless a reason for one skilled in the art to question the objective truth of the statement of utility or its scope can be established. Applicant cited case law in support of this assertion. Applicant urged that a *prima facie* case of lack of utility has not been established. Applicant argued that the examiner has not established whether or not a lack of correlation between gene copy number and protein levels is an exception to the rule or is the rule. Applicant asserted that the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. This has been carefully reconsidered but remains unpersuasive. No evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer. Indeed, evidence exists in the art that there is not always such a correlation, and thus the skilled artisan would not assume it is so, but would perform the experiment to verify it. Pennica et al. (1998, PNAS USA 95:14717-14722) supports the lack of correlation and has been discussed in the Final Office action (#16, middle of page 4). Also, Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), state that,

> "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

Finally, even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified as previously addressed (Final Office action, bottom of page 4) in the discussion of Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. Therefore, the art indicates that it is not the norm that gene amplification, or even increased transcription, results in increased protein levels. Finally, Applicant refers to the Ashkenazi declaration which asserts that if the protein levels do not increase as a result of gene amplification, it is also useful because it can serve to better diagnose the cancer. This has been fully considered but is not found to be sufficient to withdrawn the rejection, since there is no indication that the PRO339 protein levels increase or stay the same. Further research would be needed to determine PRO339 protein levels in cancers showing gene amplification of PRO339 gene. Therefore, because it cannot be concluded that the PRO339 is useful as a diagnostic marker for colon or lung cancer, neither the protein nor

antibody that specifically binds it has utility. Significant further research would be required to find out what the protein does and if and how it is linked to lung and/or colon cancer. For the reasons discussed above, the asserted utility for the claimed antibody as a diagnostic marker for identifying lung or colon cancer is not specific and substantial.

Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO339 proteins (and by extension the antibodies as claimed in this application) are simply starting points for further research and investigation into potential practical uses of the proteins and antibodies. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Therefore, the rejections under 35 U.S.C. §§ 101 and 112, first paragraph, are maintained.

35 U.S.C. § 102

Claims 39-44 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/63088 for the reasons set forth in the previous Office action on page 3.

Applicant argue that the definition of specifically binds means the antibody binds only PRO339 and no other. Even though the rejection under 35 USC 112, second paragraph, has been withdrawn, Applicant's arguments are not persuasive. While the artisan of ordinary skill would understand the meaning of specific binding in reference to an antibody, it is not agreed that specific binding means exclusive binding. Additionally, the specification does not support such a restrictive definition. For these reasons and those previously discussed, for example that PRO1281 of WO 99/63088 has a region of 18 contiguous amino acids identical to SEQ ID NO:339 of the instant application and multiple regions of at least 6 contiguous amino acids, it is

maintained that the antibodies taught by WO 99/63088 to PRO1281 anticipate the claimed invention.

35 U.S.C. § 103

Claims 39-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Sibson et al. (WO 94/01548) and Godowski et al. (US Patent 6,030,831) for the reasons set forth in the previous Office action on page 3.

Applicants argue GenBank Accession No. BAA92640 does not teach an antibody that binds a peptide. The argument has been fully considered, but is not persuasive. The rejection is one of obviousness instead of anticipation. In view of the prior art, an antibody that bound the encoded protein described by the GenBank refeence would have been obvious.

Claims 39-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Applicants' Admission on p. 34, lines 5-6 and Fleming et al. (Dev., 124:2973-81, 1997) and Godowski et al. (US Patent 6,030,831) for the reasons set forth in the previous Office action

Applicants argue that for both 35 USC 103 rejections, the instant application receives an effective filing date of 2/11/2000 due to the utility supported by gene amplification data and substantial asserted utility for the polypeptide PRO399 as discussed in the Declarations by Dr. Goddard and Dr. Ashkenazi; and, therefore, GenBank Accession No. BAA92640 is not available as prior art. The argument has been fully considered, but is not persuasive. Because of the reasons discussed above for the rejections of 35 USC 101/112, 1st paragraph, the claimed invention lacks utility. And, as previously stated, even if there is support for utility for the DNA, there is not for the polypeptide or antibody. It is maintained that the effective filing date of the instant application is 07/11/2001.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

February 4, 2004

LORRAINE SPECTOR
PRIMARY EXAMINER